Product Development and Manufacturing

"Counter Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development"

October 24, 2003

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Presentation Outline

- Overview of challenges
- Survey of some focus areas related to general manufacturing control:
  - Equipment
  - Facility / Manufacturing Environment
  - Raw Materials / Component Controls
  - Validation / Qualification Programs
  - Quality Systems
- *Product specific process development issues to follow in later presentations*

Key Challenge to Manufacturing Unit:

Due to compressed development timelines for counter bioterrorism (CBT) agents, there's a loss of development time to learn how the process behaves in routine manufacturing

Compressed Timelines for:

- Defining the process:
  - Process operating parameters and equipment SOPs complete and “road tested”?
  - Equipment supporting various unit operations qualified?
  - Experience with product allow predictability for unit operations?
- Qualification/Validation:
  - Process alteration and optimization
  - Ongoing qualification and validation (concurrent)
  - Sufficient resources?

Key Challenges to Quality Unit:

Due to compressed development timelines for counter bioterrorism (CBT) agents, there's a loss of time to get quality systems in place and to complete supporting operations!

Compressed Timelines for:

- Establishing Quality Systems:
  - Records and documentation,
  - Raw material specifications and testing procedures (sampling, sample size, test methods, etc.),
  - Vendor audit program – level of completion
  - Change control system
  - Deviation/Investigation system
- As you approach licensure….
  - Adverse event reporting system
  - Product complaints and recall systems
  - Regulatory reporting systems (supplements and BPDRs, etc.)


A QUALITY PRODUCT
QA/QC
Validation / Qualification
Routine Monitoring
Equipment
Environment
Process
Raw Materials
Components

Critical Resources to Facilitate Rapid Availability of CBT Agents

- **Very** careful choice of contract partners and vendors including "track history"

Contract Partners: Quality Agreements

- Do the quality agreements between the applicant and any contract manufacturer include adequate reporting of deviations not directly related to product manufacture?
- Example: If system failure noted covering a period bracketing contract manufacturing operation, does reporting to applicant include notification to allow assessment of impact on their product?

Contract Partners: Quality Agreements

- Does change control system of the contract manufacturer include notification of applicant and/or direct involvement of applicant in implementation decision?
- Example: Does introduction of an investigational product operation into areas utilized for contract manufacturing include applicant notification?

Critical Resources to Facilitate Rapid Availability of CBT Agents

- Experienced and knowledgeable staff – manufacturing AND quality units

Critical Resources to Facilitate Rapid Availability of CBT Agents

- Open dialog with CBER as early as possible in the planning process
- Emphasis on locking down process as rapidly as possible, *especially if early production lots intended for licensure*

Compressed timelines for addressing:

- Safety related issues:
  - Adventitious agents,
  - Maintaining sterility or bioburden control,
  - Immunogenicity concerns, etc.
- Process consistency:
  - Process alteration and optimization
  - Process scale up impacts
    - Confounded by ongoing qualification and validation activities

Some early priorities include:

- Prioritization of safety related qualification and validation activities
- Performing equipment capability assessments for each unit operation as processing parameters are defined


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Equipment: Capability Assessment - 1

- Has each unit operation been assessed for suitability of equipment and process stream contacts? (i.e., under operating conditions)
- Has each unit operation that is critical for safety of the product been validated? (e.g., sterilization of final container closure system components)

Equipment: Capability Assessment - 2

- Performance testing in place where needed? (performance capability demonstrated via appropriate qualification, validation, and/or routine manufacturing data)

Equipment: Capability Assessment - 3

- Filtration/Concentration steps validated ?
- Routine use of purification columns controlled ?
- Any rework or reprocessing steps in the process due to potential equipment function concerns ? If so, are they validated ?

Equipment: Personnel

- Personnel gowning practices appropriate?
- Personnel adequately trained ?
- Manufacturing supervisors appropriately experienced with the process ?
- Manufacturing supervisors practicing a quality approach to operations ?

Why were personnel listed under "Equipment" ?

- The process depends upon their function as specified.
- The most common cause of deviations for a well controlled process is the personnel.
- Training and qualification programs are critical


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Environment: Monitoring - 1

- Are the controlled production environments appropriately qualified and monitored for HVAC system performance and microbiological quality?
- Are the controlled production environments appropriate to support the manufacturing processes being performed ?

Environment: Monitoring - 2

- Monitoring systems adequate for open product manipulations and aseptic operations ?
- HVAC systems appropriately maintained and qualified / requalified ?
- Preventative maintenance and calibration programs appropriate ?


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Process Validation

- Do the unit operations include operating parameters based upon the validation studies?
- Does the documentation (e.g., BPR) capture all relevant operating information?

- *More detailed discussion of this topic from my colleagues speaking later this morning*


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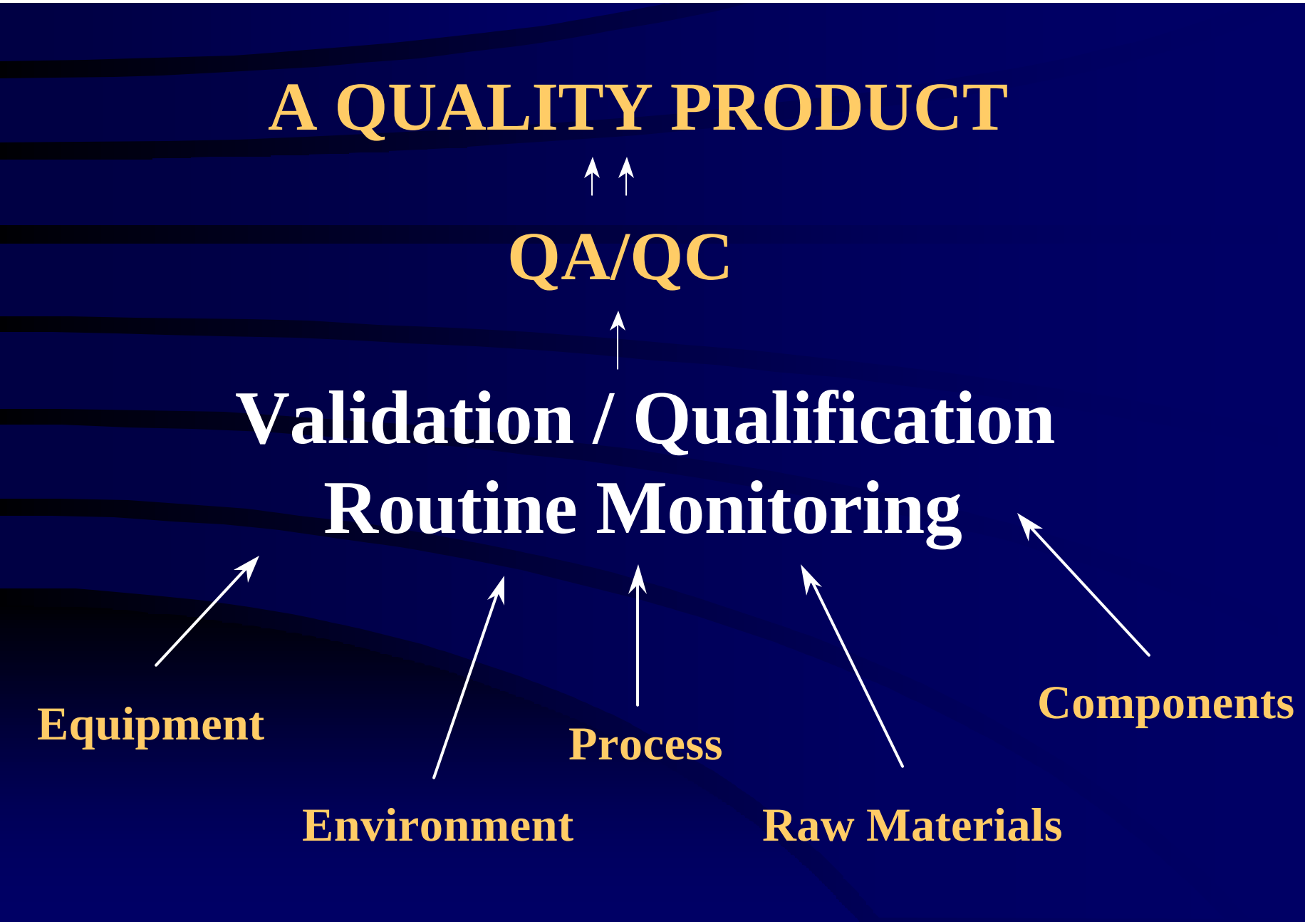
Raw Materials

- Incoming material sampling plans appropriate ?
- Acceptance criteria supported ? (i.e., fitness for use quality attributes understood)
- Vendor audits conducted for critical raw materials ?
- Quarantine / Release procedures for raw materials appropriate ?
- Quality procedures and documentation for release appropriate ?

Components

- Diluent formulation defined ?
- Clinical administration kit components that require qualification ?
- Primary packaging (container closure) system defined ?
- Contract partners for any components evaluated and qualified as a vendor ?
- Sampling programs by vendors implemented (if needed)?
- Documentation for release appropriate ?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Validation

- Sterility assurance validation studies and aseptic processing qualification studies (e.g., media challenges) completed ?
- Are cleaning validation studies appropriate for the context of use for the equipment ? Does validation approach include potential for highly biologically active cross contamination or adventitious agents (as appropriate) ?
- Are computer and PLC controlled systems appropriately controlled (and validated, if necessary) ?
- Are “closed” systems appropriately qualified ?

Validation

- How are failures handled during execution of a validation protocol ?
- Are qualification/validation studies for critical equipment systems performed appropriately ?
- Do the SOPs reflect the validated conditions for use of equipment ?

Validation: Legacy Systems

- If “legacy” equipment or facility being utilized, is the approach rigorous based upon known prior uses, or lack of prior use information?
- Have the considerations taken into account during protocol design been *documented* ?

Issues to address for lots intended for licensure

- Validation data to support processing parameters and hold times?
- Reprocessing and/or Rework procedures, if allowed?
- Conformance lots produced using the method submitted in the license application?
- Capable of successful manufacture of consecutive lots?


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Quality Systems: Documentation

- Manufacturing unit operation data recorded directly in BPR ?
- Does BPR reflect actual production ?
- Documentation for material and intermediate(s) release appropriate ?
- Final release procedures appropriate ?

Quality Systems: Issues

- How are out-of-specification (OOS) investigations handled ?
- Are deviations and investigations handled effectively ?
- Operations segregated appropriately?
- Staff adequately trained ?

Quality Systems: Testing - 1

- Method validation efforts on an appropriate timeline ?
- Are in-process and final testing samples being handled appropriately ?
- Are appropriate compendial methods in place and being performed appropriately ?

Quality Systems: Testing - 2

- Are OOS results being handled appropriately ? (i.e., investigation system triggered?)
- Are appropriate system suitability procedures in place ?
- Is testing equipment being appropriately maintained and are the records for these actions adequate ?

Quality Systems: Final Product Visual Inspection

- Does method include major and minor defect categories with alert and action limits?
- If re-inspection allowed, are there limits?
- Do visual inspectors undergo a rigorous qualification program?

Quality Systems: Vigilance for the unexpected and human factors

- Are deviations reported and are appropriate investigations performed ?
- Does the adverse event reporting system perform properly ?
- Are written procedures under change control and do staff follow the SOPs ?

Common Problem Areas for Previously Unlicensed Applicants

- Written procedures for preventative maintenance systems are lacking
- Written documentation of training programs incomplete
- Written documentation of vendor audit program incomplete, or audits not performed

Common Problem Areas for Previously Unlicensed Applicants

- Written documentation for raw materials program incomplete or ill-defined (fitness-for-use criteria not bridged from unit operation validation protocol design or results)
- Quality Operations unit backlog in final approvals of validation reports, etc. (i.e., inadequate resources for the quality operations unit or validation unit)

Common Problem Areas for Previously Unlicensed Applicants

- Does facility have design flaws relative to cGMP compliance capability? If so, can procedural control adequately support consistent manufacturing operations?

What resources are there to avoid potential pitfalls ?

Communicate with CBER and prepare throughout the process

- Guidance documents
- Feedback throughout the IND process
- Pre-submission meetings with specific questions can be very productive
- *Do not neglect manufacturing facility issues during the development process*

During the pre-BLA period….

- Be careful to have comprehensive project timelines allowing resources and time to complete facility and process related validation / qualification studies
- Let me say it again…… *Do not neglect manufacturing facility issues during the development process*

Resources

WWW Guidance Documents:
http://www.fda.gov

Phone questions for manufacturing facilities to CBER/OCBQ/DMPQ 301-827-3031

Summary

- The challenge relative to manufacturing is to have the appropriate resources to tackle the incredible number of issues that WILL arise.
  - Contract partners that have been fully evaluated
  - Excellent staffing models and expertise to draw upon (in house and external, as needed)
  - Maintain a dialog with CBER on all issues of importance

Summary

- It is critical to have an overall plan with detailed project management oversight to successfully move the product through an expedited development program on ALL fronts (i.e., pre-clinical, clinical, process development, and manufacturing)
- AND……..


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